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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,908	HINKEL ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-12 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-31* is/are rejected.

7)☒ Claim(s) *13,20 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10/03;1/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group 2, claims 13-31 in the paper mailed 6/5/03 is acknowledged. Claims 1-12 and 32-35 are withdrawn from prosecution as being directed towards non-elected inventions.

Priority

2. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional applications upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 29 and 30 of this application. The examiner was able to identify support for claims 13-28 and 31 of the instant application in the earliest filed provisional application 60/264972, filed 1/28/01. However, no basis in any of the provisional applications was identified for claims 29 and 30 which require that a single base extension is achieved by using a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label. Therefore, for these two claims, the effective filing date is the instant filing date.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 20, 21, 24, 25, 26, 27, 28, and 31, rejected under 35 U.S.C. 102(b) as being anticipated by Wallace *et al.* (WO 93/25563).

With regard to claim 20, Wallace *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one oligonucleotide primer comprising a hybridization tag that identifies said primer, said primer having a 3' end specific for a single nucleotide polymorphism of interest (p.10, beginning at line 8);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (p. 14, beginning at line 2; see also figure 4);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (p. 13-14; Figure 4);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (p. 14, beginning at line 7);

e) detecting the hybridization of said extension product to said capture probe using said detectable label (p. 14, beginning at line 13);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (p. 14, and Figure 5).

The teachings of Wallace *et al.* are considered to anticipate the claimed invention in view of the breadth of the term "particle." In the methods taught by Wallace *et al.*, the capture probes are attached to particles of a membrane filter, and the particle wherein the probe is attached identifies the probe by virtue of the location of the probe on the filter. The identity of the single nucleotide polymorphism is determined based on where the capture probe hybridizes on the filter (see Figure 5), which is interpreted as determining the identity of the single nucleotide polymorphism based on the identity of the particle.

With regard to claim 21, Wallace *et al.* teach that the present invention can be used for the determination of which alleles are present at 20 different dimorphic, genetically unlinked loci (p. 9, second paragraph), and such a method would inherently include the use of a plurality of primers each specific for a different single nucleotide polymorphism.

With regard to claim 24, Wallace *et al.* teach a method wherein the 3' end of said primer is immediately adjacent to the location of the single nucleotide polymorphism of interest (see at least figure 4).

With regard to claim 25, the method taught by Wallace *et al.* is a single base extension (see figure 4).

With regard to claim 26, the single base extension is achieved by using only a single type of nucleotide triphosphate, namely all deoxynucleotide triphosphates, and more specifically, to each extension reaction only a single labeled deoxynucleotide triphosphate was added (p. 13-14).

With regard to claims 27 and 28, Wallace *et al.* teach that the primer extension can be accomplished using chain terminating nucleotides, namely dideoxynucleoside triphosphates (p. 10, last line).

With regard to claim 31, Wallace *et al.* teach that their methods include methods for diagnosing diseases such as sickle cell anemia or thalassemia caused by a defective allele (p. 5, first full paragraph).

Thus, the teachings of Wallace *et al.* anticipate each of the rejected claims.

5. Claims 20, 21, 24, 25, 26, 27 and 28, are rejected under 35 U.S.C. 102(a) as being anticipated by Chen *et al.* (Genome Research, April 2000, 10:549-557).

With regard to claim 20, Chen *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one oligonucleotide primer comprising a hybridization tag that identifies said primer, said primer having a 3' end specific for a single nucleotide polymorphism of interest (p. 550, Col. 1, the primer has a DNA sequence at the 5' end that allows the primer to be captured onto a microbead);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (p. 556, "SBCE reactions;" Figure 1);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (p. 556, "SBCE reactions;" Figure 1);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (p. 556, "Hybridization of SBCE Reaction Mixture to Microsphere");

e) detecting the hybridization of said extension product to said capture probe using said detectable label (p. 556);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (p. 557).

With regard to claim 21, Chen *et al.* teach that the present invention can be used for the determination of which alleles are present at 4 different SNP (p. 550, Figure 2), and such a method would inherently include the use of a plurality of primers each specific for a different single nucleotide polymorphism.

With regard to claim 24, Chen *et al.* teach a method wherein the 3' end of said primer is immediately adjacent to the location of the single nucleotide polymorphism of interest (p. 556).

With regard to claim 25, the method taught by Chen *et al.* is a single base extension (i.e. the method is called "Single Base Chain Extension" throughout.).

With regard to claim 26, the single base extension is achieved by using only a single type of nucleotide triphosphate, namely all dideoxynucleotide triphosphates (p. 13-14).

With regard to claims 27 and 28, Chen *et al.* teach that the primer extension can be accomplished using chain terminating nucleotides, namely dideoxynucleoside triphosphates (p. 10, last line).

Thus, the teachings of Chen *et al.* anticipate each of the rejected claims.

6. Claims 13, 14, 15, 16, 17, 20, 21, 22, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Lai *et al.* (US 2003/0049620, filing date, 4/30/01, provisional filed 4/28/00).

With regard to claim 13, Lai *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

(a) providing at least one primer pair, said primer pair containing a reverse primer and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest and a hybridization tag that identifies the primer, said hybridization tag not complementary to the sequence containing said single nucleotide polymorphism of interest (¶ 0179);

(b) combining said at least one primer with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (¶ 0179);

(c) extending hybridized primers by primer extension to produce an extension product wherein said extension product comprises said hybridization tag and a detectable label (¶ 0179);

(d) hybridizing said extension products by said hybridization tag or the complement thereof under stringent conditions to capture a probe wherein said capture probe is coupled to a particle, said particle identifying said capture probe (¶ 0182);

(e) detecting the hybridization of said extension product to said capture probe by the presence of said detectable label (¶ 0182); and

(f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (¶ 0182).

With regard to claim 14, Lai *et al.* teach that the reverse primer comprises a detectable label (¶ 0179).

With regard to claim 15, Lai *et al.* further teach that the reverse primer is a universal primer that is universal to both alleles being tested (¶ 0185, also figure 12).

With regard to claim 16, Lai *et al.* teach repeating the extension step in subsequent rounds of PCR (¶ 0180).

With regard to claim 17, Lai *et al.* teach that this assay can be multiplexed, thus comprising a plurality of primer pairs specific for a plurality of single nucleotide polymorphisms (¶ 0183).

With regard to claim 20, Lai *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one oligonucleotide primer comprising a hybridization tag that identifies said primer, said primer having a 3' end specific for a single nucleotide polymorphism of interest (¶ 0179);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (¶ 0179, inherent in PCR);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (¶0179-0180);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (¶ 0182);

e) detecting the hybridization of said extension product to said capture probe using said detectable label (¶ 0182);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (¶ 0182).

With regard to claim 21, Lai *et al.* teach that this assay can be multiplexed, thus comprising a plurality of primer pairs specific for a plurality of single nucleotide polymorphisms (¶ 0183).

With regard to claim 22, Lai *et al.* teach a method wherein said at least one primer comprises a group of at least 2 primers, each primer specific for a different allele of a single nucleotide polymorphism of interest (¶ 0183).

With regard to claim 23, Lai *et al.* teach a method further comprising a plurality of said primer groups, each primer group specific for a different single nucleotide polymorphism of interest (¶0183).

This rejection relies on the filing date of the provisional application to support the date of the PG PUB application. If a copy of a provisional application listed on the bottom portion of the accompanying Notice of References Cited (PTO-892) form is not included with this Office action and the PTO-892 has been annotated to indicate that the copy was not readily available, it is because the copy could not be readily obtained when the Office action was mailed. Should applicant desire a copy of such a provisional application, applicant should promptly request the copy from the Office of Public Records (OPR) in accordance with 37 CFR 1.14(a)(1)(iv), paying the required fee under 37 CFR 1.19(b)(1). If a copy is ordered from OPR, the shortened statutory period for reply to this Office action will not be reset under MPEP § 710.06 unless applicant can demonstrate a substantial delay by the Office in fulfilling the order for the copy of the provisional application. Where the applicant has been notified on the PTO-892 that a copy of the provisional application is not readily available, the provision of MPEP § 707.05(a) that a copy of the cited reference will be automatically furnished without charge does not apply.

7. Claims 20, 21, 22, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Huang *et al.* (US 6287778 B1).

With regard to claim 20, Huang *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one oligonucleotide primer comprising a hybridization tag that identifies said primer, said primer having a 3' end specific for a single nucleotide polymorphism of interest (Col. 2, lines 50-55);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (Col. 2, lines 45-50);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (Col. 2, lines 55-57);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (Col. 2, lines 57-59);

e) detecting the hybridization of said extension product to said capture probe using said detectable label (Col. 4, lines 14-16);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (Col. 5, lines 43-52).

With regard to claim 21, Huang *et al.* teach that this assay can be multiplexed, thus comprising a plurality of primers specific for a plurality of single nucleotide polymorphisms (Col. 4, lines 20-25).

With regard to claim 22, Huang *et al.* teach a method wherein said at least one primer comprises a group of at least 2 primers, each primer specific for a different allele of a single nucleotide polymorphism of interest (Col. 17, lines 55-60; Claim 15).

With regard to claim 23, Huang *et al.* teach a method further comprising a plurality of said primer groups, each primer group specific for a different single nucleotide polymorphism of interest (Col. 4, lines 20-25).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 13, 14, 15, 16, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace *et al.* (US5639611) in view of Gerry *et al.* (J. Molecular Biology, 292:251-262 (1999)).

With regard to claim 13, Wallace *et al.* (US) teach a method for detecting a single nucleotide polymorphism comprising:

(a) providing at least one primer pair, said primer pair containing a reverse primer and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest (Col. 2, lines 20-25; Col. 3, lines 50-57);

(b) combining said at least one primer with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (Col. 4, lines 1-5);

(c) extending hybridized primers by primer extension to produce an extension product wherein said extension product comprises said hybridization tag and a detectable label (Col. 4, lines 1-5);

Wallace *et al.* (US) further teach the capture of PCR products using a biotin-streptavidin interaction for the detection of a particular allele (Col. 3, lines 20-25).

With regard to claim 14, Wallace *et al.* (US) teach that either the forward or the reverse primer can contain a detectable label (Col. 6, lines 60-65).

With regard to claim 15, Wallace *et al.* (US) further teach that the reverse primer is a universal primer that is universal to both alleles being tested (Col. 3, lines 50-60, the BGP2 primer is used as the reverse primer for both alleles).

With regard to claim 16, Wallace *et al.* (US) teach repeating the extension step in multiple rounds of PCR (Col. 4, lines 5-10).

With regard to claim 19, Wallace *et al.* (US) exemplify the method for the detection of sickle cell anemia alleles, and specifically teach a method for diagnosing sickle cell anemia (Col. 3-4; Claim 3).

Wallace *et al.* (US) do not teach a method wherein the forward primer comprises a hybridization tag that identifies the primer, said hybridization tag not complementary to the sequence containing the single nucleotide polymorphism of interest, nor do they teach hybridizing extension products via the tag to a probe coupled to a particle, detecting the hybridization and identifying the single nucleotide polymorphism based upon the identity of said particle. Wallace *et al.* further do not teach a method wherein the at least one primer pair comprises a plurality of primer pairs specific for a plurality of single nucleotide polymorphisms.

Gerry *et al.* teach a universal DNA microarray method for multiplex detection of point mutations. In the methods taught by Gerry *et al.* allele specific primers are utilized which comprise a 3' end specific for an allele of a single nucleotide polymorphism of interest and a 5' that comprises a hybridization tag that identifies the primer, said hybridization tag no complementary to the sequence containing said single nucleotide polymorphism of interest (Figure 1(a); Table 3). After an allele specific reaction (in this case, ligase detection reaction), the reacted primers are hybridized to a capture probe and detected via a detectable label (p. 260, second column). The location of the detection spot on the array (i.e. the identity of the particle to which the capture probe is coupled) identifies the polymorphism and allele present in the sample (p. 257, Figure 3).

With regard to claim 17, Gerry *et al.* teach a plurality of primers that are specific for a plurality of single nucleotide polymorphisms (p. 260).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Wallace *et al.* so as to have used the binary primer (having an allele specific portion and a hybridization tag) taught by Gerry *et al.* One would have been motivated to have modified the method taught by Wallace *et al.* in order to take advantage of the benefit of the "zip-code" arrays taught by Gerry *et al.*, who teach, "Since the zip-code sequences remain constant, and their complement can be appended to any set of LDR primers, our zip-code arrays are universal. Thus, a single array can be programmed to detect a wide range of genetic mutations...The universal zip-code array approach introduced here has the potential to allow rapid and reliable identification of low abundance mutations in multiple codons of numerous genes (p. 258-259)." Thus, the use of the zip-code methodologies taught by Gerry *et al.* with the methods of Wallace *et al.* would have afforded one of ordinary skill in the art the opportunity to expand the methods taught by Wallace *et al.* for the detection of multiple mutations and codons.

11. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.* (Clinical Chemistry, 43(9):1749-1756 (1997)).

Lai *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

(a) providing at least one primer pair, said primer pair containing a reverse primer and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest and a hybridization tag that identifies the primer, said hybridization tag not

complementary to the sequence containing said single nucleotide polymorphism of interest (¶ 0179);

(b) combining said at least one primer with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (¶ 0179);

(c) extending hybridized primers by primer extension to produce an extension product wherein said extension product comprises said hybridization tag and a detectable label (¶ 0179);

(d) hybridizing said extension products by said hybridization tag or the complement thereof under stringent conditions to capture a probe wherein said capture probe is coupled to a particle, said particle identifying said capture probe (¶ 0182);

(e) detecting the hybridization of said extension product to said capture probe by the presence of said detectable label (¶ 0182); and

(f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (¶ 0182).

In the methods taught by Lai *et al.*, the capture probe is attached to a particle that is a microsphere (¶0181).

Lai *et al.* do not teach a method wherein the detection is by flow cytometry. (For clarity of the record, it is noted that Lai *et al.* at ¶ 0264 do teach detection by flow cytometry. However, this disclosure is not supported by Lai *et al.*'s provisional application, which support is relied upon in this rejection).

Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization

methodologies (p. 1753-1755). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Lai *et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.* One would have been motivated to utilize such methodology because Fulton *et al.* teach that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that their system "...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy (p. 1775)." Thus, one would have been motivated to use flow cytometry to detect the microspheres taught by Lai *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

12. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lai *et al.* in view of Wallace *et al.* (WO 93/25563).

Lai *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

(a) providing at least one primer pair, said primer pair containing a reverse primer and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest and a hybridization tag that identifies the primer, said hybridization tag not complementary to the sequence containing said single nucleotide polymorphism of interest (¶ 0179);

(b) combining said at least one primer with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (¶ 0179);

(c) extending hybridized primers by primer extension to produce an extension product wherein said extension product comprises said hybridization tag and a detectable label (¶ 0179);

(d) hybridizing said extension products by said hybridization tag or the complement thereof under stringent conditions to capture a probe wherein said capture probe is coupled to a particle, said particle identifying said capture probe (¶ 0182);

(e) detecting the hybridization of said extension product to said capture probe by the presence of said detectable label (¶ 0182); and

(f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (¶ 0182).

Lai *et al.* do not teach the application of this methodology for diagnosing a disease, condition, disorder or predisposition. However, at the time the invention was made, it was routine in the prior art to utilize the detection of single nucleotide polymorphisms for the detection of any number of diseases. For example, Wallace *et al.* teach the detection of diseases such as sickle cell anemia or thalassemia caused by a defective allele (p. 5, first full paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the methods taught by Lai *et al.* for the detection of disease as suggested by Wallace *et al.* in order to have provided a method for detecting diseases caused by single nucleotide polymorphisms.

13. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace *et al.* in view of Gerry *et al.* as applied to claims 13, 14, 15, 16, 17, and 19 above, and further in view of Fulton *et al.*

The teachings of Wallace *et al.* in view of Gerry *et al.* are discussed in the previous 103 rejection and are applied to claim 18 as discussed therein. These do not teach a method wherein the detection occurs by flow cytometry.

Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization methodologies (p. 1753-1755). Fulton *et al.* teach the multiplexed assays which utilize the microspheres are suitable for use with oligonucleotide target molecule (p. 1750), and teach that with respect to hybridization assays that the no-wash format of many microsphere-based assays, particularly in the final detection step, is considerably faster than assays that require multiple washings (p. 1755). They also teach that the rapid kinetics of micrsphere-based assays that allow shorter incubation times than conventional solid supports (p. 1755).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Wallace *et al.* in view of Gerry *et al.* so as to have provided a microsphere based assay that included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.* One would have been motivated to utilize such methodology because Fulton *et al.* teach that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that their system "...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy (p. 1775)." Thus, one would have been motivated to use flow cytometry to detect the microspheres taught by Wallace *et al.* in view of Gerry *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

14. Claims 22-23 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* in view of Dubiley *et al.* (Nucleic Acids Research, 1999, Vol. 23, No. 18, page e19).

Chen *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one oligonucleotide primer comprising a hybridization tag that identifies said primer, said primer having a 3' end specific for a single nucleotide polymorphism of interest (p. 550, Col. 1, the primer has a DNA sequence at the 5' end that allows the primer to be captured onto a microbead);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (p. 556, "SBCE reactions;" Figure 1);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (p. 556, "SBCE reactions;" Figure 1);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (p. 556, "Hybridization of SBCE Reaction Mixture to Microsphere");

e) detecting the hybridization of said extension product to said capture probe using said detectable label (p. 556);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (p. 557).

Chen *et al.* teach that the present invention can be used for the determination of which alleles are present at 4 different SNP (p. 550, Figure 2), and such a method would inherently include the use of a plurality of primers each specific for a different single nucleotide polymorphism.

With regard to claim 22, Chen *et al.* do not teach a method wherein said at least one primer comprises a group of at least 2 primers, each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest. With regard to claim 31, Chen *et al.* do not teach or suggest the application of these methodologies to the detection of disease or conditions.

Dubiley *et al.* teach a single nucleotide extension method for the detection of polymorphic alleles which utilized primers that contain different 3'-terminal nucleotide overlapping the variable DNA, and teach a group of at least 2 primers, each primer having a 3' end specific for different alleles of a single nucleotide polymorphism of interest (heading: Materials and Methods; Isothermal single base primer extension assay; Identification of a single base polymorphism with multiprimer assay). In the multiprimer assay, four primers variable at the 3' nucleotide are used to test all four possible bases in the polymorphic site of target DNA (heading: RESULTS; Amplified multibase and multiprimer single-stranded extension). Furthermore, Dubiley *et al.* teach the application of single base extension methodologies to β-Thalassemia diagnosis (heading: RESULTS; β-Thalassemia diagnostics).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the primers taught by Dubiley *et al.* in the methods taught by Chen *et al.* so as to have provided a method which utilizes a pair of at least two primers, each

primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest, and further to have utilized the polymorphism detection methods for the detection of disease related alleles. The use of such primers would have provided an alternate methodology for the detection of single nucleotide polymorphisms using the basic methodology taught by Chen *et al.*, as Dubiley *et al.* teach that the use of primers that end adjacent to or overlap with the polymorphic site have comparable specificity with regard to one another (final page, first full paragraph). The use of the method for the detection of disease alleles would provide the obvious benefit of detecting disease alleles and thus the presence or predisposition to disease.

15. Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* in view of Söderlund *et al.* (US 6013431).

Chen *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one oligonucleotide primer comprising a hybridization tag that identifies said primer, said primer having a 3' end specific for a single nucleotide polymorphism of interest (p. 550, Col. 1, the primer has a DNA sequence at the 5' end that allows the primer to be captured onto a microbead);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (p. 556, "SBCE reactions;" Figure 1);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (p. 556, "SBCE reactions;" Figure 1);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (p. 556, "Hybridization of SBCE Reaction Mixture to Microsphere");

e) detecting the hybridization of said extension product to said capture probe using said detectable label (p. 556);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (p. 557).

Chen *et al.* teach a method wherein the 3' end of said primer is immediately adjacent to the location of the single nucleotide polymorphism of interest (p. 556) and the method taught by Chen *et al.* is a single base extension (i.e. the method is called "Single Base Chain Extension" throughout).

While Chen *et al.* utilize labeled chain terminating nucleoside triphosphates, namely dideoxynucleoside triphosphates, Chen *et al.* do not teach a method wherein a plurality of chain-terminating nucleoside triphosphates (p. 555), each comprising a unique label are used, as is recited in claims 29 and 30.

Söderlund *et al.* teach single nucleotide primer extension methods which a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used for the detection of more than one point mutation occurring at the same site out of one undivided sample (Col. 8, lines 44-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Chen *et al.* so as to have included differentially labeled ddNTPs as taught by Söderlund *et al.* within the reaction mixture in order to detect more than one point mutation occurring at the same site of an undivided sample.

16. Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace (WO'93) *et al.* in view of Söderlund *et al.*

Wallace *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one oligonucleotide primer comprising a hybridization tag that identifies said primer, said primer having a 3' end specific for a single nucleotide polymorphism of interest (p.10, beginning at line 8);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (p. 14, beginning at line 2; see also figure 4);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (p. 13-14; Figure 4);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (p. 14, beginning at line 7);

e) detecting the hybridization of said extension product to said capture probe using said detectable label (p. 14, beginning at line 13);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (p. 14, and Figure 5).

In the methods taught by Wallace *et al.*, the capture probes are attached to particles of a membrane filter, and the particle wherein the probe is attached identifies the probe by virtue of the location of the probe on the filter. The identity of the single nucleotide polymorphism is determined based on where the capture probe hybridizes on the filter (see Figure 5), which is interpreted as determining the identity of the single nucleotide polymorphism based on the identity of the particle.

With regard to claim 24, Wallace *et al.* teach a method wherein the 3' end of said primer is immediately adjacent to the location of the single nucleotide polymorphism of interest (see at least figure 4).

With regard to claim 25, the method taught by Wallace *et al.* is a single base extension (see figure 4).

While Wallace *et al.* teach methods which utilize labeled chain terminating nucleoside triphosphates, namely dideoxynucleoside triphosphates (p. 10, last line), Wallace *et al.* do not teach a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used, as is recited in claims 29 and 30.

Söderlund *et al.* teach single nucleotide primer extension methods which a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique

label are used for the detection of more than one point mutation occurring at the same site out of one undivided sample (Col. 8, lines 44-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Wallace *et al.* so as to have included differentially labeled ddNTPs as taught by Söderlund *et al.* within the reaction mixture in order to detect more than one point mutation occurring at the same site of an undivided sample.

Claim Objections

17. Claims 13, 20, and 24 objected to because of the following informalities:

Claim 13 is objected to because it recites "wherein said extension product comprising said hybridization tag and a detectable label," in step (c) of the claim, and this language appears to be a grammatical error. It would be more appropriate if the claim recited that the extension product "comprises" the recited elements.

Claim 20 is objected to because it recites "said capture probe couple to a particle" in part (d) of the claim and it appears the claim should recite "is coupled" for the proper tense.

Claim 24 is objected to because it recites that the primer is "immediately adjacent to location" and it appears that a word is missing from this phrase.

Appropriate correction is required.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

Please note that on January 13, 2003 the examiner's telephone number will change to (571) 272-0753.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (703) 308-1119. Beginning January 13, 2003 Gary Benzion's telephone number will be (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196. Beginning January 13, 2003 the receptionist's telephone number will be (571)272-0507.

Juliet C Switzer
Examiner
Art Unit 1634

December 22, 2003